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Reply to 'Why mechanical dyssynchrony remains relevant to cardiac resynchronization therapy'

We are delighted to be given the opportunity to respond to the letter by Puvrez *et al.* and clarify the current role of imaging in the selection of patients for cardiac resynchronization therapy (CRT). The aim of our manuscript, which was endorsed by the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and the European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology, was to offer practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on easy actionable domains and describe the clinical research evidence underlying these.[1] The document includes a section on imaging of potential CRT candidates but clearly outlines and supports the current practical and evidence-based guidelines that limit selection to the presence of left ventricular systolic dysfunction (with an ejection fraction <35%) and electrocardiographic evidence of conduction delay.[2]

On the whole we do not disagree with the statements made by Puvrez *et al.* but some clarification is required. Firstly, Puvrez *et al.* contest the statement that patients fulfilling the guidelines who do not have mechanical dyssynchrony should still receive a CRT device yet then contradict themselves by commenting that it would be 'undesirable to withhold CRT from patients with a wide left bundle branch block'. This is entirely in keeping with the guidelines and the aim of our manuscript. Whilst visible pre-implant mechanical dyssynchrony is associated with a greater chance of acute haemodynamic improvement following CRT, the lack of dyssynchrony should not be used to de-select patients otherwise eligible.[1]

Interestingly, the works cited by Puvrez *et al.* describe the effect of electrical dyssynchrony on chamber mechanics and that imaging might in due course help discern which patients *outside* of the current guidelines might benefit from CRT. Crucially, the studies referenced are observational and include only implanted patients. The data therein cannot therefore identify the true benefit of CRT on clinical outcomes in such patients. Moreover, remodelling endpoints, although related to outcomes, firstly, are by their nature binary, a somewhat unlikely clinical scenario and secondly fail to appreciate that the relationship between remodelling and clinical events following CRT is markedly different across aetiologies (a patient with ischaemic heart disease gains a greater prognostic benefit from a given degree of remodelling than one with a non-ischaemic cardiomyopathy). Hence a non-responder to an arbitrary echocardiographic cut-off might still gain clinical benefit. These issues underscore the importance of randomized clinical trials with parallel group allocation, and blinded analysis of patient-orientated clinical outcomes including in pre-specified subgroups focusing on patients lying outside the current guidelines.

We are puzzled by the comment that 'there is no significant difference in survival between the different recommendations including class III evidence'. The current guidelines are based upon randomized clinical studies and as a population, patients with a current contraindication (class III) for implantation do not gain benefit. However, we agree entirely with Purvez *et al.* that patients with a QRS duration <150 ms require additional consideration, but it is far too early to advocate simply treating 'more patients with a QRS ≥130 ms who show left ventricular mechanical dyssynchrony regardless of QRS morphology'. This is contrary to the current guidelines.[2] We would strongly encourage further randomized clinical trials in CRT, possibly using novel dyssynchrony evaluation (as proposed by Puvrez *et al.*) to select candidates outside the current guidelines that gain benefit on hard clinical endpoints of heart failure hospitalization and mortality. This is critical, because previous data have shown that although pre-implant mechanical dyssynchrony is, not unexpectedly, associated with more reverse remodelling, there is no evidence of a greater effect on patient-relevant clinical endpoints.

Finally, we agree entirely with Puvrez *et al.* that the concept of 'cost-effectiveness' is dependent upon perspective. The incremental cost-effectiveness ratio (ICER) over medical therapy is €7538 for CRT with a pacemaker (CRT-P) and €18 017 for CRT with a defibrillator (CRT-D).[1] But the ICER for CRT-D vs. CRT-P is much greater. On balance, this makes CRT-P the most cost-effective device-based intervention in cardiology and more cost-effective than the medical treatment of hypertension or angioplasty for stable angina.[3] Nevertheless, utilization of these devices is indeed hampered by their perceived upfront cost in low-income countries. We take issue, however, with the comment that further imaging, itself associated with a cost, could de-select individuals currently indicated for CRT, or select patients currently not indicated. The proposed tools are not proven to be able to do this. A reasonable alternative would be to consider tighter personalization of the current blanket provision of CRT-D, driven largely by reimbursement arrangements, which could markedly reduce the cost of CRT to society. This would require improved clinical interpretation of pre-implant characteristics including imaging information[1] and preferably data from a clinical trial that can be used to inform guidelines.

Wilfried Mullens[1]*, Pieter Martens[1], Klaus Witte[2], and Martin R. Cowie[3]

[1]Ziekenhuis Oost Limburg, Genk, University Hasselt, Hasselt, Belgium; [2]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; and [3]Imperial College London, Royal Brompton Hospital, London, UK
*Email: wilfried.mullens@zol.be

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